General

Guideline Title

Practice guideline summary: treatment of restless legs syndrome in adults: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology.

Bibliographic Source(s)

Winkelman JW, Armstrong MJ, Allen RP, Chaudhuri KR, Ondo W, Trenkwalder C, Zee PC, Gronseth GS, Gloss D, Zesiewicz T. Practice guideline summary: treatment of restless legs syndrome in adults: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2016 Dec 13;87(24):2585-93. [60 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- August 31, 2016 – Opioid pain and cough medicines combined with benzodiazepines : A U.S. Food and Drug Administration (FDA) review has found that the growing combined used of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. FDA is adding Boxed Warnings to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines.

Recommendations

Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I-IV) are provided at the end of the "Major Recommendations" field.

Recommendations

1. In moderate to severe primary restless legs syndrome (RLS), clinicians should consider prescribing a pharmacologic agent to reduce RLS symptoms. There is strong evidence to support the use of pramipexole, rotigotine, cabergoline, and gabapentin enacarbil (Level A); moderate evidence to support the use of ropinirole, pregabalin, and intravenous (IV) ferric carboxymaltose (FCM) (Level B); and weak evidence to support the use of levodopa (Level C). There are few head-to-head comparisons of these agents to suggest that one should be used preferentially, though in practice clinicians often decide on the basis of comorbidities or potential side effects such as augmentation with dopaminergic agents. When considering efficacy alone, clinicians may consider choosing cabergoline instead of levodopa (Level C). However, cabergoline is rarely used in clinical practice for RLS because of a risk of cardiac valvulopathy at higher doses. There is insufficient evidence to support or refute the preferential use of pregabalin instead of pramipexole (Level U).
2. For patients with primary RLS for whom clinicians want to target sleep, clinicians should consider prescribing a pharmacologic agent that improves objective or subjective sleep parameters (or both). Evidence supports agents to different extents for subjective and objective outcomes.
    a. When targeting periodic limb movements of sleep (PLMS), specifically the Periodic Limb Movement Index (PLMI) as measured by polysomnography (PSG), there is strong evidence to support the use of ropinirole (Level A); moderate evidence to support the use of pramipexole, rotigotine, cabergoline, and pregabalin (Level B); and weak evidence to support the use of levodopa (Level C). There is insufficient evidence to support or refute the use of gabapentin enacarbil, FCM, or iron sucrose for PLMS (Level U). There is weak evidence (Level C) for using pramipexole in preference to pregabalin with regard to PLMI alone.
    b. With regard to other objective sleep measures (e.g., total sleep time [TST], sleep efficiency, sleep latency, and wake after sleep onset [WASO]), there is moderate evidence to support the use of ropinirole, gabapentin enacarbil, and pregabalin for at least some objective sleep measures (Level B). There is insufficient evidence to support or refute the use of pramipexole, rotigotine, cabergoline, or levodopa for these measures (Level U). There is weak evidence (Level C) for using pregabalin in preference to pramipexole with regard to objective sleep measures other than PLMI.
    c. With regard to subjective sleep measures, there is strong evidence to support the use of cabergoline and gabapentin enacarbil (Level A); moderate evidence to support the use of ropinirole, pramipexole, and pregabalin (Level B); weak to moderate evidence to support the use of rotigotine (Levels B and C); and weak evidence to support the use of levodopa (Level C), with the strength of evidence varying by measure and, sometimes, dose. There is insufficient evidence to support or refute the use of FCM for subjective sleep measures (Level U). There is moderate evidence to support the use of pregabalin instead of pramipexole with regard to subjective sleep outcomes (Level B).
3. For patients with RLS for whom clinicians want to target concomitant psychiatric symptoms, clinicians should consider ropinirole in the context of anxiety (Level B) and may consider ropinirole in the context of depression (Level C). In the context of moderate to severe RLS-related mood disturbance, clinicians may consider prescribing pramipexole for depression and anxiety (Level C). For overall mood, clinicians should consider prescribing gabapentin enacarbil (Level B).
4. For patients with RLS for whom clinicians want to select an agent that improves quality of life (QoL), clinicians should consider prescribing ropinirole, pramipexole, cabergoline, gabapentin enacarbil, or IV FCM (Level B) and may consider prescribing rotigotine or pregabalin (Level C). There is insufficient evidence to support or refute the use of levodopa for improving QoL in RLS (Level U).
5. When avoidance of augmentation is a deciding factor, clinicians may consider prescribing pregabalin rather than pramipexole when considering 52-week treatment in light of lower augmentation rates with pregabalin (Level C). Clinicians may also consider prescribing cabergoline rather than levodopa when considering 30-week treatment in light of lower augmentation rates with cabergoline (Level C); however, this needs to be weighed against the risk of cardiac valvulopathy with high doses of cabergoline. There is insufficient evidence to support or refute which dopaminergic agents cause the least augmentation because augmentation rates are most commonly reported in long-term open-label Class IV studies (Level U). Results of these studies are summarized in the full guideline at Neurology.org but cannot support formal recommendations.
6. For patients with RLS who have not responded to other treatments, clinicians may consider prescribing prolonged-release oxycodone/naloxone (where available) for RLS symptoms, subjective sleep symptoms, and QoL (Level C), but potential benefits need to be weighed against known opioid risks.
7. There is insufficient evidence to support or refute the use of gabapentin, iron sucrose, oxycodone, clonazepam, bupropion, clonidine, selenium, rifaximin, botulinum neurotoxin, valproic acid, carbamazepine, or valerian in the treatment of RLS (Level U).
8. For patients or clinicians wanting to use nonpharmacologic approaches to treat RLS, clinicians should consider prescribing pneumatic compression before usual symptom onset (Level B) and may consider prescribing near-infrared spectroscopy (NIRS) or repetitive transcranial magnetic stimulation (rTMS) (where available) (Level C). Clinicians may consider prescribing vibrating pads for subjective sleep concerns (Level C) but not for RLS symptoms (Level C against). Clinicians may also choose not to consider transcranial direct current stimulation for RLS symptoms (Level C against). There is insufficient evidence to support or refute use of acupuncture in RLS (Level U).
9. In patients with RLS and serum ferritin ≤75 μg/L, clinicians should consider prescribing ferrous sulfate 325 mg with vitamin C 200 mg for improvement of RLS symptoms (Level B).
10. In patients with secondary RLS associated with end-stage renal disease (ESRD) on hemodialysis (HD), clinicians should consider

prescribing vitamin C and E supplementation (alone or in combination) (Level B) and may consider prescribing ropinirole, levodopa, or exercise (Level C). There is insufficient evidence to support or refute the use of gabapentin or IV iron dextran in RLS associated with ESRD/HD (Level U). There is also insufficient evidence to support or refute the use of gabapentin or levodopa preferentially over the other in this population (Level U).

Definitions

Classification of Evidence for Risk of Bias

Therapeutic Scheme

Class I

A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
    1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority
    2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
    3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment
    4. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers

Class II

A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV

Studies not meeting Class I, II, or III criteria, including consensus or expert opinion.

*Numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Classification of Recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Restless legs syndrome (RLS)

Guideline Category

Assessment of Therapeutic Effectiveness

Management

Treatment

Clinical Specialty

Family Practice

Hematology

Nephrology

Neurology

Psychiatry

Sleep Medicine

Intended Users

Physicians

Guideline Objective(s)

- To make evidence-based recommendations regarding restless legs syndrome (RLS) management in adults
- To address the following question: What are safe and effective therapies, including both pharmacologic and non-pharmacologic approaches, for the symptoms and clinical consequences (disturbed sleep, periodic limb movements of sleep [PLMS], depression/anxiety, and decreased quality of life [QoL]) of RLS in adults?

Target Population

Adult patients with restless legs syndrome (RLS)

Interventions and Practices Considered

1. Pharmacologic therapy
    - Dopamine agonists
        - Ropinirole
        - Pramipexole
        - Rotigotine patch
        - Cabergoline
        - Levodopa
    - Alpha 2 delta ligands
        - Pregabalin
        - Gabapentin
        - Gabapentin enacarbil
    - Iron treatments
        - Ferrous sulfate (oral iron)
        - Intravenous ferric carboxymaltose
    - Opioid agonists (prolonged-release oxycodone/naloxone)
2. Non-pharmacologic therapy
    - Pneumatic compression
    - Near-infrared spectroscopy (NIRS)
    - Repetitive transcranial magnetic stimulation (rTMS)
    - Vibratory stimulation (vibrating pads)
    - Transcranial direct current stimulation (tDCS) (considered but not recommended)
3. Treatment of secondary RLS
    - Vitamin C and E supplementation
    - Pharmacologic therapy (i.e., ropinirole, levodopa)
    - Exercise

Note: There is insufficient evidence to recommend the use of gabapentin, iron sucrose, oxycodone, clonazepam, bupropion, clonidine, selenium, rifaximin, botulinum neurotoxin, valproic acid, carbamazepine, valerian or acupuncture for treatment of RLS.

Major Outcomes Considered

- Measures of restless legs syndrome (RLS)
    - International Restless Legs Syndrome Study Group rating scale (IRLS)
    - Restless Legs Syndrome-6 Scale (RLS-6)
- Measures of sleep
    - Periodic Limb Movement Index (PLMI)
    - RLS-6
    - Medical Outcomes Study (MOS) Sleep Scale
    - Total sleep time (TST)
    - Sleep efficiency
    - Sleep latency
    - Wake after sleep onset (WASO)
- Comorbidities (e.g., mood and anxiety disorders, loss of work productivity)
- Quality of life (QoL)
- Adverse effects of pharmacological agents, especially augmentation risk

Methodology

Methods Used to Collect/Select the Evid

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Panel members developed the clinical question, the data extraction template, and the search terms. An independent medical librarian performed a systematic literature search in all languages in December 2007 (refer to appendix e-3 in the data supplement [see the "Availability of Companion Documents" field] for the complete search strategy) for pharmacologic and non-pharmacologic restless leg syndrome (RLS) therapies. Three databases (MEDLINE, EMBASE, and Science Citation Index) were searched from 1966 to December 2007. The guideline panel subsequently performed an identical search in order to include articles published from December 2007 to August 2011. The independent librarian performed a final identical search in July 2015. The chair of the panel reviewed each of the retrieved 2,729 abstracts to establish whether an article met the basic inclusion criteria: (1) original article described treatment of RLS, (2) study lasted longer than a single night (for each treatment arm), and (3) article was not a single-patient case report.

Number of Source Documents

Refer to the "Analysis of Evidence" sections in the guideline and the Data Supplement (see the "Availability of Companion Documents" field) for number of studies included for each topic.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence for Risk of Bias

Therapeutic Scheme

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The following are also required:

a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
    1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority
    2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
    3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment
    4. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers

Class II

A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV

Studies not meeting Class I, II, or III criteria, including consensus or expert opinion.

*Numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Articles meeting basic criteria were reviewed and classified by 2 panel members, working independently of each other, for quality of evidence on the basis of the American Academy of Neurology (AAN) therapeutic classification scheme rating risk of bias pertaining to study characteristics (see the "Rating Scheme for the Strength of the Evidence" field). Two additional committee members adjudicated discrepancies between reviewers. Studies involving only interventions that have been withdrawn from the market (e.g., pergolide, which was removed from the market in the United States in 2007 because of concerns regarding associated valvulopathy) were excluded. Recommendations were derived from the conclusions and are strictly tied to the evidence (see the "Rating Scheme for the Strength of the Recommendations" field).

For each intervention, data were extracted for results regarding efficacy for restless leg syndrome (RLS) symptoms and efficacy for sleep, mood, and quality of life (QoL). For RLS efficacy, the International Restless Legs Syndrome Study Group rating scale (IRLS) was the preferred outcome, if available, and a change of 3 points was considered clinically meaningful. For sleep outcomes, the most commonly used subjective scales were the RLS-6 and the Medical Outcomes Study (MOS) Sleep Scale, for which clinically meaningful changes have not been established. The MOS Sleep Scale includes 4 subscales: sleep disturbance (decrease indicates improvement), sleep quantity (in hours; increase indicates improvement), sleep adequacy (increase indicates improvement), and daytime somnolence (decrease indicates improvement). For studies reporting Post Sleep Questionnaire (PSG) results, the panel chose to evaluate the Periodic Limb Movement Index (PLMI), total sleep time (TST), sleep efficiency, sleep latency, and wake after sleep onset (WASO) for uniformity between studies. PLMI is a PSG measure calculated by dividing the total number of PLMS by sleep time in hours. The clinical importance of PLMI is uncertain, however, and optimal PSG parameters for assessing clinically meaningful changes in sleep in RLS have not been established.

Even in the face of uncertainty regarding the clinical importance of any given change score on sleep and QoL measures, when considering these outcomes, one must assess not only statistical significance but also clinical relevance in order to decide whether a given result should inform a conclusion for or against use of an agent for that outcome or whether the evidence is insufficient to draw conclusions. Statistical significance, clinical significance, and precision were all considered when deriving conclusions from the evidence. This resulted in 6 possible outcomes, 4 occurring in the context of statistical significance and 2 occurring when there is not statistical significance:

1. The point estimate of the difference between 2 interventions is clinically important, and the confidence interval (CI) around this point estimate is both statistically significant and clinically important: conclusion developed in favor of the superior intervention.
2. The point estimate of the difference between 2 interventions is clinically important, and the CI is statistically significant but include values that are not clinically important or are of uncertain clinical relevance: conclusion developed in favor of the superior intervention, but text includes a description of the limitation in interpretation due to CIs.
3. The point estimate of the difference between 2 interventions is *not* clinically important, but the difference is statistically significant and the CI includes a clinically important difference: conclusion states insufficient evidence because the point estimate is not clinically important

(regardless of statistical significance), but CIs include a difference that is clinically important, so clinical importance remains possible.
4. The point estimate of the difference between 2 interventions is *not* clinically important, the difference is statistically significant, and the CI includes only values that also are not clinically important: conclusion states that the 2 interventions are essentially equivalent because the difference between them is not clinically important; if one of the interventions is placebo, conclude that the active intervention does not result in a clinically meaningful improvement.
5. The difference between 2 interventions is *not* statistically significant, and the CI does *not* include clinically important values: conclusion states that the active intervention does not result in benefit vs the comparator.
6. The difference between 2 interventions is *not* statistically significant, but the CI includes clinically important (or potentially clinically important) values: conclude that there is insufficient evidence because, although the results were not statistically significant, there remains the possibility for an important difference between interventions (this is often the case when studies have insufficient precision [e.g., because they are underpowered]).

With the exception of the IRLS, where a 3-point difference was considered clinically meaningful/relevant, these judgments were made by guideline panel members on the basis of a subjective assessment of the change (e.g., a difference of 30 minutes of night sleep was considered to be potentially clinically important; an odds ratio [OR] CI including 1.01 was perceived to include an OR of dubious clinical importance). Provided or calculated CIs are available for most referenced articles (where data are sufficient to calculate CIs if they were not provided) so that readers can assess whether their judgments align with those made by the guideline panel. The practice guideline indicates when the CIs include values of potential or uncertain clinical relevance. The six categories just presented are most relevant when considering the IRLS, where a clinically important difference was prespecified. In the case of sleep and QoL outcomes, assessment of CIs was most relevant in cautioning against overinterpretation of conclusions in favor of an agent (item 2 in the previous list) or when attempting to decide whether a result that was not statistically significant had a narrow enough CI to recommend against use or whether there was insufficient evidence (items 5 and 6 in the list). Ultimately, readers can derive their own conclusions from review of the provided CIs.

Evidence-based medicine methodology consultants performed random-effects meta-analyses when there was a need to reconcile potentially discordant results or improve statistical precision. For the purpose of establishing confidence in the evidence, results of meta-analyses were considered equivalent to the classification of the contributing studies. For example, if a meta-analysis was performed on 2 Class I studies but only one of those studies had statistical significance, the results of that meta-analysis were considered equivalent to a single Class I study. If a meta-analysis was performed on Class I and Class II studies and none of the studies achieved statistical significance on their own, the results of that meta-analysis were deemed equivalent to a single Class II study.

Results are presented for each dose according to the results extracted from reviewed studies. For the formulation of conclusions, the decision was made to write conclusions for the medication rather than considering each dose separately. This decision was based on the assumption that clinicians will follow prescribing instructions, which typically start at the smallest recommended dose and gradually titrate up to clinical effect, using the lowest effective dose to try to limit dose-dependent side effects. U. S. Food and Drug Administration (FDA)-approved doses for each recommended medication are included in table e-1 of the online Data Supplement (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This practice guideline follows the methodologies outlined in the 2004 edition of the American Academy of Neurology's (AAN's) guideline development process manual (see the "Availability of Companion Documents" field). In 2007, the Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) of the AAN assembled a panel of clinicians and investigators from the United States and Europe who had published extensively on restless legs syndrome (RLS) and who represented a broad range of relevant expertise and opinion.

Recommendations were based on conclusions and class of evidence in accordance with the AAN process (see the "Rating Scheme for the Strength of the Recommendations" field), where Level A reflects strong evidence, Level B reflects moderate evidence, and Level C reflects weak evidence. A Level U recommendation represents insufficient evidence to support or refute the use of any given intervention. Class I and II articles are described in the text of the original guideline document (in cases with substantial Class I evidence, Class II evidence is referenced but not described); Class III studies are described only if there are insufficient articles with a higher classification to drive conclusions and recommendations. Class IV studies are not described except in the context of side effects and long-term complications, particularly augmentation.

Rating Scheme for the Strength of the Recommendations

Classification of Recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Cost Analysis

A formal cost analysis was not performed, and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Drafts of the guideline have been reviewed by at least 3 American Academy of Neurology (AAN) committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields.

The guideline was approved by the Guideline Development, Dissemination, and Implementation Subcommittee on November 7, 2015; by the Practice Committee on December 21, 2015; and by the AAN Institute Board of Directors on August 29, 2016.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Reduction in restless legs syndrome (RLS)-related symptoms
- Improvement in sleep parameters
- It is possible that ropinirole improves depression and likely that it improves anxiety at 12 weeks. It is possible that pramipexole improves depression and anxiety at 12 weeks in patients with moderate to severe RLS-related mood disturbance. It is likely that gabapentin enacarbil improves overall mood.
- Refer to the Data Supplement (see the "Availability of Companion Documents" field) for discussions of each intervention regarding efficacy

for RLS symptoms and efficacy for sleep, mood, and quality of life.

Potential Harms

- Augmentation is a major side effect of long-term treatment of restless legs syndrome (RLS) with dopaminergic medication (levodopa and dopamine agonists). Augmentation refers to an iatrogenic worsening of RLS and is most commonly characterized by an advance of symptom onset by at least 2 to 4 hours. It may also be manifested by increased intensity of RLS symptoms, wider anatomical distribution, shorter latency to symptom onset, or shorter duration of medication benefit. Its likelihood of occurrence increases with longer duration of dopaminergic medication use; it does not usually occur before 6 months of treatment.
- In addition to the risk of augmentation for dopaminergic agent, it is now recognized that some agents for RLS have less common but important risks. These risks include not only cardiac valvulopathy with cabergoline but also side effects such as impulse control disorders with the dopamine agonists. The augmentation risk and other common or important adverse events of interventions considered in the guideline are summarized in a table in the original guideline document.
- Another potential limitation of long-term pharmacologic treatment of RLS is loss of efficacy.
- Benefits of opioid use must be weighed against risks such as potential abuse.

Qualifying Statements

Qualifying Statements

Refer to the "Clinical Context" section of the original guideline document for a discussion of the limitations of the evidence and unresolved issues.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Winkelman JW, Armstrong MJ, Allen RP, Chaudhuri KR, Ondo W, Trenkwalder C, Zee PC, Gronseth GS, Gloss D, Zesiewicz T. Practice guideline summary: treatment of restless legs syndrome in adults: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2016 Dec 13;87(24):2585-93. [60 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Dec 13

Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

Source(s) of Funding

This guideline was developed with financial support from the American Academy of Neurology (AAN). Authors who serve or served as AAN subcommittee members or methodologists were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

Guideline Committee

Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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Financial Disclosures/Conflicts of Interest

Conflict of Interest

The American Academy of Neurology (AAN) is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. The AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects.

Disclosures

J. Winkelman currently serves on scientific advisory boards for Merck and Flex Pharma and has served on scientific advisory boards for UCB, Impax, Pfizer, Lacrima, Luitpold Pharmaceuticals, GlaxoSmithKline, Boehringer-Ingelheim, Xenoport, Zeo Inc., Sunovion, Insys, Takeda, Jazz, and Neurogen; currently performs neurophysiology studies as part of his practice; currently serves as a journal editor for the following publications: *Sleep*, *Sleep Medicine*, and *CNS Drugs*; has received honoraria from or served on speakers bureaus for the following organizations: Boehringer-Ingelheim, GlaxoSmithKline, Pfizer, Sepracor (now Sunovion), Takeda, Luitpold Pharmaceuticals, Novartis, Neurogen, and UCB (Schwarz Pharma); has received research support from Boehringer-Ingelheim, GlaxoSmithKline, UCB (Schwarz Pharma), Sepracor (now Sunovion), and Pfizer; holds stock in Flex Pharma; receives publishing royalties for the following publications: *Foundations of Psychiatric Sleep Medicine* (Cambridge University Press, 2010) and an UpToDate chapter on nocturnal leg cramps; receives government research support from the National Institute of Mental Health (1RO1MH095792-01A1, PI); and has given expert testimony for legal cases representing generic manufacturers of pharmaceuticals approved for the treatment of insomnia and narcolepsy. M. Armstrong receives compensation from the American Academy of Neurology (AAN) as an evidence-based medicine methodologist and serves on the Level of Evidence editorial board for *Neurology* but is not compensated financially. R. Allen has served on a volunteer basis for the International Restless Legs Syndrome Study Group and the World Association of Sleep Medicine; has served on scientific advisory boards for Pfizer, GlaxoSmithKline, Boehringer Ingelheim, Jazz Pharmaceuticals, UCB, Luitpold, and Xenoport; has received funding for travel from UCB; currently serves as a field editor for the journal *Sleep Medicine*; has served as a journal editor for the following journals: *Sleep Medicine*, *Sleep*, and *Movement Disorders*; receives publishing royalties from *Sleep* and *Movement Disorders*; has received honoraria from UCB for CME; currently serves as a consultant for Luitpold Pharmaceuticals; holds a patent (PCT/US15/15556) for a device and method for detection of periodic leg movements; and has received research support from GlaxoSmithKline, Pharmacosmos, and the NIH. K. Chaudhuri has served as a journal editor-in-chief for *Nature Parkinson Journal* and as editor for *Basal Ganglia*; receives publishing royalties from the following publications: *Non-Motor Symptoms of Parkinson's Disease*, Oxford University Press, 2nd edition, 2014, and 1st edition, 2011; has received honoraria from Parkinson's UK, the National Institute of Health Research (NIHR), the International Parkinson and Movement Disorder Society, Parkinson's UK and EU, and UCB, and for sponsored symposiums from UCB, AbbVie, Britannia, US Worldmeds, Otsuka, Medtronic, and Zambon; has served as a consultant for AbbVie, UCB, Britannia, Medtronic, and Mundipharma; currently serves on a scientific advisory board for Mundipharma and has served on a scientific advisory board for Eli Lilly in April of 2013; has received research support from Britannia and UCB (in the form of educational grants), from the NIHR (UK and EU both, for development of a nonmotor symptoms questionnaire for RLS), and from Parkinson's UK (in the form of the following awards: 2016–2018: Horizon 2020 award: i-PROGNOSIS: Intelligent Parkinson Early Detection Guiding Novel Supportive Interventions, 2015–2016: CRN South London contingency funding, and 2014–2016: International Parkinson's and Movement Disorders Society: Field Validation of the MDS-NMS Scale); and currently receives license fee payments for the following scales: the King's Parkinson's Disease Pain Scale and the revised Parkinson's Disease Sleep Scale. W. Ondo serves on speakers bureaus for Teva, Lundbeck, Merz, UCB, Xenoport, and Avanir; has received research support in the form of grants from USWorld Meds, Cynapsus, Dystonia Coalition, Tremor Research Group, Huntington Study Group, Auspex, and InSightec; serves on the *Neurology* Level of Evidence editorial advisory board; and receives royalties for co-editing the UpToDate

publication *Restless Legs Syndrome*. C. Trenkwalder has served on scientific advisory boards for Britannia, UCB, Mundipharma, Novartis, Vifor, and Desitin; has received honoraria from UCB, Mundipharma, Desitin, Britannia, and GlaxoSmithKline; has received grants from Teva, Mundipharma, Horizon 2020 European Frame Work Program, and the Michael J. Fox Foundation; has served as an investigator for Mundipharma, Novartis, and Vifor; has received research support from Mundipharma and Teva; and has received publishing royalties from Schattauer for *Parkinson* and from Thieme (Georg Thieme Verlag) for *Parkinson Disease* and for guidelines on RLS from the German Neurological Society. P. Zee currently serves on scientific advisory boards for Merck, Phillips, and Eisai; has served on scientific advisory boards for Sanofi, Merck, Aptalis, Jazz, Vanda, Ferring, Takeda, UCB, Purdue, Pernix, and Phillips; serves as the deputy editor for *Sleep* and for the *Journal of Sleep Medicine*; has served as an associate editor for *Sleep* and as single-issue editor for the journal *Sleep Medicine Clinics*; holds a patent on a light therapy visor; receives publishing royalties from Wolters Kluwer for various books; has received honoraria from Merck, Aptalis, Jazz, Vanda, and Ferring; has received research support from Boehringer Ingelheim Pharmaceuticals, Inc. and GlaxoSmithKline for studies related to RLS, and from Takeda Pharmaceuticals, Jazz, Philips Consumer Lifestyle International B.V., the NIH, the American Academy of Sleep Medicine, and Northwestern Memorial Foundation (for studies not related to RLS); serves on the American Board of Internal Medicine test-writing committee for the Sleep Medicine Board Exam; has received honoraria for numerous speaking engagements; and has held stock in Teva. G. Gronseth serves as an associate editor for *Neurology* and as an editorial advisory board member of *Neurology Now*, and receives compensation from the AAN for work as the chief evidence-based medicine methodologist. D. Gloss serves as an evidence-based medicine consultant for the AAN. T. Zesiewicz serves on the editorial boards of *Tremor and Other Hyperkinetic Disorders* and *Neurodegenerative Disease Management* and has received research support for work on the Friedreich's Ataxia Research Alliance. Go to Neurology.org for full disclosures.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

A list of American Academy of Neurology (AAN) guidelines, along with a link to this guideline, is available from the AAN Web site.

Availability of Companion Documents

The following are available:

- Practice guideline: treatment of restless legs syndrome in adults: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Data supplement (e-appendices, e-references, e-tables). St. Paul (MN): American Academy of Neurology; 2016 Nov. 72 p. Available from the Neurology Journal Web site.
- Practice guideline: treatment of restless legs syndrome in adults: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Slide presentation. St. Paul (MN): American Academy of Neurology; 2016 Nov. 45 p. Available from the American Academy of Neurology (AAN) Web site.
- Practice guideline: treatment of restless legs syndrome in adults: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Summary of evidence-based guideline for clinicians. St. Paul (MN): American Academy of Neurology; 2016 Nov. 4 p. Available from the AAN Web site.
- American Academy of Neurology (AAN). Clinical practice guideline process manual, 2004 Ed. St. Paul (MN): American Academy of Neurology. 2004. 57 p. Available from the AAN Web site.

Patient Resources

The following is available:

- Treatment of restless legs syndrome in adults. Summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology; 2016 Nov. 3 p. Available from the American Academy of Neurology (AAN) Web site.

NGC Status

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